Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Hughes TP, Mauro MJ, Cortes JE, et al. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. N Engl J Med 2019;381:2315-26. DOI: 10.1056/NEJMoa1902328

Supplementary Appendix

Contents

Investigators

Timothy P. Hughes, M.D.	Investigator	Australia
Michael J. Mauro, M.D.	Investigator	United States
Jorge E. Cortes, M.D.	Investigator	United States
Hironobu Minami, M.D.	Investigator	Japan
Delphine Rea, M.D.	Investigator	France
Daniel J. DeAngelo, M.D., Ph.D.	Investigator	United States
Massimo Breccia, M.D.	Investigator	Italy
Yeow-Tee Goh, M.D.	Investigator	Singapore
Moshe Talpaz, M.D.	Investigator	United States
Andreas Hochhaus, M.D.	Investigator	Germany
Phillipp Le Coutre, M.D.	Investigator	Germany
Oliver Ottmann, M.D.	Investigator	United Kingdom
Michael C. Heinrich, M.D.	Investigator	United States
Juan Luis Steegmann, M.D., Ph.D.	Investigator	Spain
Michael W.N. Deininger, M.D., Ph.D.	Investigator	United States
Jeroen J.W.M. Janssen, M.D., Ph.D.	Investigator	The Netherlands
Francois-Xavier Mahon, M.D.	Investigator	France
Yosuke Minami, M.D., Ph.D.	Investigator	Japan
David Yeung, M.D.	Investigator	Australia
David Ross, M.D.	Investigator	Australia
Martin S. Tallman, M.D.	Investigator	United States
Jae H. Park, M.D.	Investigator	United States
Brian J. Druker, M.D.	Investigator	United States
Fabian Lang, M.D.	Investigator	Germany
Dong-Wook Kim, M.D., Ph.D.	Investigator	South Korea

Supplementary Methods

Study Oversight

The full protocol is available at NEJM.org. The study was conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation. The protocol was approved by relevant institutional review boards or ethics committees, and all participants gave written informed consent.

Study Design

The ABL001X2101 study was an open label, non-randomized study, and the information presented herein comes from one part of the larger study. In dose escalation, treatment included twice-daily dosing of asciminib administered continuously over 28-day cycles. On the basis of pharmacokinetics (PK) data from early cohorts, the protocol was amended to administer asciminib once daily. Patients continued asciminib until disease progression, unacceptable toxicity, investigator decision, or withdrawal of patient's consent.

Assessment of Safety

Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.01. Dose-limiting toxicities (DLTs) assessed during cycle 1 were defined as grade ≥3 nonhematologic toxicities lasting >3 days despite adequate supportive care, missed doses owing to toxicity accounting for >25% of cycle 1, or febrile neutropenia not related to disease. Hematologic dose-limiting adverse events were grade 4 cytopenia not related to disease and lasting >42 days, with bone marrow examination revealing <5% cellularity.

Methods of Pharmacokinetics Analyses

Blood samples were collected and evaluated in all patients at all dose levels. Full PK profiles were obtained from patients in the dose-escalation cohorts on their first day of dosing and after repeated administration in weeks 2 and 4 (cycle 1 day 15 and cycle 2 day 1, respectively). In addition, trough (predose) visits were assessed every 4 weeks during the first 6 months of treatment. Plasma concentrations of asciminib were measured using a validated liquid chromatography–tandem mass spectrometry assay with a limit of quantification of 1.0 ng/mL. PK parameters were determined with a noncompartmental method using Phoenix WinNonlin (Pharsight, Mountain View, CA) software version 6.4. Patients were categorized according to the actual dose and regimen on the day of the laboratory analysis for intensive PK days. An integrated analysis of all PK data was performed applying nonlinear mixed-effects modeling in Monolix 4.3.2.

A preliminary population-based, 2-compartment PK-pharmacodynamics (PD) model with linear elimination and distribution was used to assist in the selection of a recommended dose. Absorption was described by a zeroth-order absorption process followed by a first-order absorption process. A semiphysiological model was developed to describe BCR-ABL1 molecular response kinetics according to the International Scale (IS). This model mimics leukemic cell maturation by a chain of compartments between immature cells and circulating cells, reproduces disease progression by an immature leukemic cell exponential growth, and accounts for existing resistance by separating a pool of sensitive cells from a pool of resistant immature cells. The drug killing rate on immature, sensitive leukemic cells was set proportionally to the asciminib concentration. A secondary parameter, average clinical concentration for stable disease, was derived as the ratio of immature leukemic cell growth rate by the potency parameter. PK parameter estimates from the population PK model were used to simulate PK profiles at various doses (20, 40, and 80 mg twice daily) to determine a dose that resulted in steady-state trough concentrations above average clinical concentrations for stable disease. In addition, parameter estimates from the PD model were used to perform simulations to determine the percentage of patients likely to achieve a 1-$\log_{10}$ reduction in BCR-ABL1 mRNA transcripts at the selected recommended dose. Simulations were performed at various doses (20, 40, and 80 mg twice daily) to determine a dose that resulted in steady-state trough concentrations above preclinical thresholds.

Assessment of Antileukemic Activity

Molecular, cytogenetic, and hematologic responses were defined according to standard criteria and summarized according to the patient's disease status (chronic phase [CP] vs accelerated phase [AP]) and baseline mutational status (with T315I mutation vs no T315I mutation detected). Hematologic and cytogenetic responses were assessed at the investigators' institutional laboratories. Response rates (percentages in the tables) were calculated using the number of evaluable patients as the denominator. Achievement of a response was assessed for patients who did not meet the response criteria at baseline. Maintenance of a response was assessed for patients who had met the response criteria at baseline.

Major molecular response (MMR) was defined as a value of ≤0.1% BCR-ABL1 on the IS. The MMR rate by 6 or 12 months was defined as the proportion of patients whose best molecular response by a specific visit was at least MMR, ie, if a patient achieved MMR but then lost it before or at a specific visit, he or she was still classified as having achieved MMR by that specific time point. In calculation of the MMR rate by 6 months, a patient was evaluable if he or she received ≥1 dose of asciminib and met 1 of these conditions:

- Was exposed to asciminib for ≥6 months (168 study days) and had a postbaseline assessment of BCR-ABL1 transcript at 5 or 6 months (study day between 126 and 181 inclusive, considering the visit window), or
- Achieved MMR before being treated for 6 months (early responders), or
- Discontinued treatment for any reason before 6 months without achieving MMR. These patients were counted as nonresponders

The evaluable patients for MMR rate by 12 months were defined in a similar fashion.

Further categories of molecular response are defined based on the IS:

- BCR-ABL1 >10%
- 1% < BCR-ABL1 ≤10%
- 0.1% < BCR-ABL1 ≤1%
- 0.01% < BCR-ABL1 ≤0.1%
- BCR-ABL1 ≤0.01%

Complete cytogenetic response (CCyR) was defined as a value of 0% Philadelphia chromosome–positive (Ph+) metaphases in the bone marrow. Cytogenetic response was assessed in all patients at baseline. At the postbaseline visits, the assessment of Ph+ metaphases did not have to be performed if the achievement of CCyR could be supported by the BCR-ABL1 ratio. For patients whose cytogenetic response data were missing, the BCR-ABL1 ratio ≤ 1% (IS) was imputed as achieving CCyR. **Partial cytogenetic response (PCyR)** was defined as >0% and ≤35% Ph+ metaphases in the bone marrow. PCyR was not imputed based on the BCR-ABL1 ratio. **Major cytogenetic response (MCyR)** was defined as the achievement of either CCyR or PCyR.

The CCyR, PCyR, or MCyR rates presented in Table 3 are the proportion of evaluable patients whose best cytogenetic response was CCyR, PCyR, or MCyR during the treatment period. A patient was evaluable if he or she received ≥1 dose of asciminib and had ≥1 postbaseline assessment of cytogenetic response or BCR-ABL1 transcript. The analysis was performed only in Ph+ patients.

A **complete hematologic response (CHR)** was defined based on European LeukemiaNet criteria. Investigators assessed the hematologic response status of all patients at baseline: CHR or hematologic relapse, as well as any post-treatment change from CHR to loss of CHR, or vice versa. A BCR-ABL1 ratio ≤5% (IS) or achievement of normalized complete blood count was imputed as achievement of a CHR when the investigator's assessment was not available. The CHR rate presented in Table 3 is the proportion of evaluable patients who achieved CHR during the treatment period

(improvement from CHR relapse at baseline). A patient was evaluable if he or she was in hematologic relapse at baseline, received ≥1 dose of asciminib, and had ≥1 postbaseline assessment of hematologic response or BCR-ABL1 transcript.

Statistical Analysis

The current analysis included patients who commenced asciminib before September 1, 2017. The maximum tolerated dose (MTD) was defined as the highest drug dosage that had a <25% risk of causing a dose-limiting–toxicity event in >33% of the treated patients during the first cycle. Safety and efficacy data were summarized for all patients with CP–chronic myeloid leukemia (CP-CML) and AP-CML who received ≥1 dose of asciminib. PK analyses were based on data from patients in the dose-escalation phase. Two patients with CP-CML who were reported to have baseline T315I mutations did not have T315I mutations detected by the central laboratory and were enrolled in the study after having been treated with only 1 prior tyrosine kinase inhibitor. The primary analysis method was a 2-parameter Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle. The EWOC principle mandated that a dose may be used for newly enrolled subjects only if the risk of excessive toxicity, ie, ≥ 33%, at that dose is < 25%. The DLT relationship was described by the following logistic regression model:

$$\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*),$$

$$\alpha_1, \beta_1 > 0$$

where $\text{logit}(\pi_1(d_1)) = \ln(\pi_1(d_1)/(1-\pi_1(d_1)))$. $\pi_1(d_1)$ is the probability of a DLT if asciminib was given to patients with CML as a single agent at dose d_1, where d_1 represented the total daily dose. Doses were rescaled as d_1/d_1^* with reference dose d_1^* = 300 mg total daily dose of asciminib. As a consequence, α_1 was equal to the odds of toxicity at d_1^*. Only DLTs occurring during the first cycle of treatment were considered in the BLRM.

Supplementary Results

Development of New Myristoyl Pocket Mutations in Patients With CP-CML and AP-CML

A patient with AP-CML with a baseline V299L mutation and resistance to dasatinib and nilotinib received asciminib 40 mg twice daily. The patient achieved CHR by day 42 and a reduction in BCR-ABL1 transcripts from >10% at baseline to 1.6% by day 90. The patient progressed to blast phase within 2 months in association with newly detected myristoyl pocket I502L and V468F mutations. A second patient with CP-CML with T315I and BCR-ABL1^{IS} >10% developed P465S (8%) and G109D (3.3%) myristoyl pocket mutations at week 72 of treatment. A third patient with CP-CML with T315I and BCR-ABL1^{IS} >10% developed A337T (37%), G463D (8.7%), and Y115N (5%) myristoyl pocket mutations at week 58 of treatment. At the time of the analysis, both of the latter 2 patients remained on study treatment (stable BCR-ABL1^{IS} >10%).

Patients Who Experienced Progressive Disease on Asciminib

Of the 17 patients with CP-CML or AP-CML who discontinued asciminib due to progressive disease, only 4 were deemed to be responders as defined by achieving ≥1-log reduction in their BCR-ABL1^{IS} transcript level. Two of these 4 patients are highlighted in Figure S5 (patients number 1 and 2) and discussed in the Results section of the text (subsection on Development of Myristoyl Pocket Mutations); 1 additional patient experienced disease progression as a result of noncompliance with administration of asciminib, and a second patient with a baseline E279K mutation in BCR-ABL1 and hematologic disease showed early progression after 5 months of asciminib and discontinued asciminib after 11 months with cytogenetic disease and without ever having achieved MMR. Of the other 13 nonresponding patients with progressive disease, all displayed hematologic and/or cytogenetic levels of disease at baseline and were discontinued from study due to their inability to achieve ≥1-log reduction in their BCR-ABL1^{IS} or to achieve MMR in order to pursue other therapies. Of this group, 6 patients had baseline T315I mutations, 5 patients had nonmutated BCR-ABL1 at baseline (1 patient each noted to have b3a3 or b2a3 BCR-ABL1 transcripts), and 1 patient each had a L248V/G250E/V299L co-occurring mutation or a M244V mutation. Patients received asciminib for anywhere between 3 and 30 months before discontinuing asciminib.

Supplementary Tables

Table S1. Geometric Mean ± CV Pharmacokinetics Parameters of Asciminib Following Oral Administration: Single Dose and Steady State.*

Week	Day	Treatment Group	N	T_{max}, hr†	C_{max}, ng/mL	AUC_{last}, ng•hr/mL‡	Trough (predose visit), ng/mL
Single dose: week 1	Day 1	10 mg BID	1	3.0	123	534	
		20 mg BID	14	2.1 (1.8 to 3.1)	233 (39)	990 (41)	
		40 mg BID	31	2.1 (1.0 to 5.6)	506 (68)	2095 (63) n = 30	
		80 mg BID	12	2.9 (1.0 to 3.9)	1285 (37)	5458 (37)	
		150 mg BID	13	2.0 (1.9 to 4.0)	2278 (51)	10,414 (43)	
		160 mg BID	2	3.4 (0.83 to 6.0)	2326 (222)	8310 (245)	
		200 mg BID	8	2.0 (1.0 to 3.9)	3748 (44)	14,635 (41)	
		80 mg QD	15	2.2 (1.8 to 6.0)	1154 (49)	5000 (51)	
		120 mg QD	16	2.1 (1.2 to 3.1)	1973 (26)	8384 (26)	
		200 mg QD	11	2.0 (1.1 to 4.0)	3718 (37)	15,987 (34)	
Steady state: week 2	Day 1	10 mg BID	1	2.2	211	1010	53
		20 mg BID	5	3.0 (2.0 to 4.1)	325 (34)	1792 (35)	102 (52) n = 13
		40 mg BID	12	2.1 (2.0 to 4.0)	718 (57)	3786 (53)	253 (83) n = 27
		80 mg BID	11	2.1 (2.0 to 3.0)	2046 (29)	10,908 (41)	768 (100) n = 12
		150 mg BID	12	2.0 (1.9 to 4.1)	3573 (43)	19,871 (55)	1763 (65) n = 11
		160 mg BID	2	2.6 (2.2 to 3.0)	5178 (32)	29,011 (22)	2855 (43)
		200 mg BID	6	2.1 (2.0 to 4.0)	6843 (30)	36,925 (28)	2384 (123) n = 8
		80 mg QD	12	3.0 (1.2 to 4.4)	1422 (33)	6715 (28)	152 (181) n = 13
		120 mg QD	15	2.1 (1.9 to 3.0)	2153 (30)	10,127 (28)	308 (46)
		200 mg QD	7	2.1 (1.9 to 4.0)	3966 (39)	19,528 (37)	484 (207) n = 9
Steady state: week 4	Day 1	10 mg BID	1	2.0	169	707	46
		20 mg BID	12	2.1 (1.3 to 6.0)	340 (65)	1750 (64) n = 11	89 (83) n = 13
		40 mg BID	28	2.0 (1.0 to 4.1)	806 (47)	3957 (43)	265 (64) n = 29
		80 mg BID	11	2.0 (1.5 to 4.0)	2030 (40)	10,813 (48)	712 (110) n = 12
		150 mg BID	12	2.0 (2.0 to 3.0)	3261 (44)	17,329 (54)	1532 (41)
		160 mg BID	2	2.0 (1.9 to 2.0)	6928 (22)	38,298 (3.9)	3423 (4.8)
		200 mg BID	6	1.9 (1.0 to 3.9)	6466 (51)	33,480 (40)	2646 (40) n = 7
		80 mg QD	12	2.0 (1.1 to 4.1)	1795 (25)	8015 (23)	183 (61) n = 11
		120 mg QD	15	2.0	2359 (27)	10,298 (29)	292 (54)

				(1.0 to 3.3)			
		200 mg QD	9	2.0 (2.0 to 3.0)	4239 (49)	19,242 (46)	538 (47)

* AUC_{last} denotes the area under the curve up to the last measurable concentration, BID twice daily, C_{max} maximum concentration, CV coefficient of variation, QD once daily, T_{last} time of last measurable concentration, and T_{max} time to maximum concentration.

† The median and range are reported.

‡ T_{last} for BID was 8 or 12 hours depending on the time when the last pharmacokinetics sample was collected; for QD, T_{last} was 24 hours.

Table S2. Demographic and BCR-ABL1 Mutational Status at Baseline.*

	Patients With Chronic-Phase CML					Patients With Accelerated-Phase CML	
	Non-T315I			T315I		Non-T315I	T315I
	BID	QD	Combined QD + BID	200 mg BID	Combined QD + BID	Combined QD + BID	Combined QD + BID
Age							
Median (range) — yr	54 (25 to 78)	57 (27 to 88)	56 (25 to 88)	67 (33 to 76)	54 (23 to 76)	61 (40 to 75)	53 (27 to 77)
≥65 yr — no. (%)	13 (19)	15 (33)	28 (25)	5 (56)	10 (36)	2 (50)	1 (20)
Sex — no. (%)†							
Male	38 (56)	19 (42)	57 (50)	7 (78)	19 (68)	2 (50)	5 (100)
Female	30 (44)	25 (56)	55 (49)	2 (22)	9 (32)	2 (50)	0
BCR-ABL1 mutational status — no. (%)							
No mutation detected	**58 (85)**	**43 (96)**	**101 (89)**	**0**	**0**	**3 (75)**	**0**
No sequencing data‡	16 (24)	16 (36)	32 (28)	0	0	2 (50)	0
No mutation per sequencing analysis	42 (62)	27 (60)	69 (61)	0	0	1 (25)	0
1 mutation	**9 (13)**	**1 (2)**	**10 (9)**	**7 (78)**	**22 (79)**	**1 (25)**	**5 (100)**
T315I	0	0	0	7 (78)	22 (79)	0	5 (100)
F317L	3 (4)	0	3 (3)	0	0	0	0
E255K	2 (3)	0	2 (2)	0	0	0	0
E279K	1 (1)	0	1 (1)	0	0	0	0
G250E	1 (1)	0	1 (1)	0	0	0	0

V299L	1 (1)	0	1 (1)	0	0	0	0
Y253H	1 (1)	0	1 (1)	0	0	0	0
M244V	0	1 (2)	1 (1)	0	0	1 (25)	0
≥2 mutations	**1 (1)**	**1 (2)**	**2 (2)**	**2 (22)**	**6 (21)**	**0**	**0**
G83T, T315I	0	0	0	1 (11)	1 (3.6)	0	0
T315I, F359V	0	0	0	0	1 (3.6)	0	0
T315I, M351T	0	0	0	0	1 (3.6)	0	0
T315I, E355G	0	0	0	1 (11)	1 (3.6)	0	0
T315I, F359I	0	0	0	0	1 (3.6)	0	0
Y253H, T315I	0	0	0	0	1 (3.6)	0	0
M244V, G250E	0	1 (2)	1 (1)	0	0	0	0
L248V, G250E, V299L	1 (1)	0	1 (1)	0	0	0	0

* BID denotes twice daily, CML chronic myeloid leukemia, and QD once daily. Percentages were based on the number of patients who received ≥1 dose of asciminib.

† Sex was unknown for 1 patient with chronic phase CML (non-T315I, QD schedule).

‡ Included no amplification, no transcript detected, not evaluable, and missing.

Table S3. Serious Adverse Events, Regardless of Study Drug Relationship.*

Preferred Term	Asciminib Monotherapy for Patients With CP-CML or AP-CML (N = 150)	
	All Grades, no. (%)	Grade 3/4 no. (%)
Total†	54 (36.0)	37 (24.7)
Pleural effusion	5 (3.3)	3 (2.0)
Pneumonia	3 (2.0)	3 (2.0)
Atrial fibrillation	2 (1.3)	2 (1.3)
Bronchospasm	2 (1.3)	2 (1.3)
Myocardial infarction	2 (1.3)	2 (1.3)
Noncardiac chest pain	2 (1.3)	1 (0.7)
Pancreatitis	2 (1.3)	1 (0.7)
Peripheral arterial occlusive disease	2 (1.3)	2 (1.3)
Pyrexia	2 (1.3)	0
Sepsis	2 (1.3)	2 (1.3)
Abdominal pain	1 (0.7)	0
Acinetobacter bacteremia	1 (0.7)	1 (0.7)
Acute coronary syndrome	1 (0.7)	1 (0.7)
Acute kidney injury	1 (0.7)	0
Acute pulmonary edema	1 (0.7)	1 (0.7)
Alanine aminotransferase increased	1 (0.7)	1 (0.7)
Amylase increased	1 (0.7)	1 (0.7)
Angina pectoris	1 (0.7)	1 (0.7)
Appendicitis perforated	1 (0.7)	1 (0.7)
Arrhythmia	1 (0.7)	1 (0.7)
Arterial bypass occlusion	1 (0.7)	1 (0.7)
Asthenia	1 (0.7)	0
Atypical pneumonia	1 (0.7)	1 (0.7)
Bone pain	1 (0.7)	1 (0.7)

Breast cancer	1 (0.7)	1 (0.7)
Bronchiolitis	1 (0.7)	0
Candida infection	1 (0.7)	1 (0.7)
Cardiac failure congestive	1 (0.7)	1 (0.7)
Cardiovascular disorder	1 (0.7)	1 (0.7)
Cerebellar infarction	1 (0.7)	0
Cerebrovascular accident	1 (0.7)	0
Chest pain	1 (0.7)	0
Cholecystitis	1 (0.7)	1 (0.7)
Cholecystitis acute	1 (0.7)	1 (0.7)
Chronic obstructive pulmonary disease	1 (0.7)	1 (0.7)
Circulatory collapse	1 (0.7)	1 (0.7)
Cyanosis	1 (0.7)	1 (0.7)
Diabetes mellitus inadequate control	1 (0.7)	1 (0.7)
Dyspnea	1 (0.7)	1 (0.7)
Enterocolitis	1 (0.7)	0
Fall	1 (0.7)	1 (0.7)
Gastritis	1 (0.7)	1 (0.7)
Gastroesophageal reflux disease	1 (0.7)	0
General physical condition abnormal	1 (0.7)	1 (0.7)
Hematuria	1 (0.7)	1 (0.7)
Hemolytic anemia	1 (0.7)	1 (0.7)
Hemiparesis	1 (0.7)	1 (0.7)
Hypersensitivity	1 (0.7)	0
Inflammation	1 (0.7)	1 (0.7)
Influenza	1 (0.7)	1 (0.7)
Intestinal obstruction	1 (0.7)	1 (0.7)
Kidney infection	1 (0.7)	1 (0.7)
Leukocytosis	1 (0.7)	1 (0.7)
Liver disorder	1 (0.7)	1 (0.7)
Malignant melanoma	1 (0.7)	1 (0.7)
Multiple organ dysfunction syndrome	1 (0.7)	1 (0.7)

Myalgia	1 (0.7)	1 (0.7)
Myelodysplastic syndrome	1 (0.7)	0
Myocardial ischemia	1 (0.7)	1 (0.7)
Nephrolithiasis	1 (0.7)	1 (0.7)
Osteonecrosis	1 (0.7)	0
Pancreatitis acute	1 (0.7)	0
Peripheral ischemia	1 (0.7)	1 (0.7)
Peripheral vascular disorder	1 (0.7)	1 (0.7)
Pleurisy	1 (0.7)	0
Pneumonia klebsiella	1 (0.7)	1 (0.7)
Post procedural infection	1 (0.7)	1 (0.7)
Pulmonary embolism	1 (0.7)	1 (0.7)
Pulmonary edema	1 (0.7)	1 (0.7)
Renal failure	1 (0.7)	1 (0.7)
Respiratory failure	1 (0.7)	1 (0.7)
Respiratory syncytial virus infection	1 (0.7)	1 (0.7)
Rhabdomyolysis	1 (0.7)	1 (0.7)
Septic shock	1 (0.7)	1 (0.7)
Stasis dermatitis	1 (0.7)	0
Tetany	1 (0.7)	1 (0.7)
Thrombocytopenia	1 (0.7)	1 (0.7)
Upper gastrointestinal hemorrhage	1 (0.7)	1 (0.7)
Urinary tract infection	1 (0.7)	1 (0.7)
Urticaria	1 (0.7)	0
Viral hepatitis carrier	1 (0.7)	0
Vomiting	1 (0.7)	1 (0.7)

* AP denotes accelerated phase, CML chronic myeloid leukemia, and CP chronic phase.

† Included all patients who received ≥1 dose of asciminib.

Table S4. Molecular Responses With Asciminib in Patients With CP-CML or AP-CML Analyzed by Reported Resistance to or Intolerance of Prior TKI Therapy.*

Major molecular response, n/N† (%)	Non-T315I				T315I			
	All Patients	Intolerant	Resistant to Ponatinib	Resistant to Other TKI	All Patients	Intolerant	Resistant to Ponatinib	Resistant to Other TKI
BID + QD	(N = 85)‡	(N = 44)‡	(N = 5)‡	(N = 31)‡	(N = 33)‡	(N = 2)‡	(N = 12)‡	(N = 15)‡
By 6 months	31/72 (43)	27/37 (73)	0/4	3/28 (11)	5/24 (21)	0/1	1/8 (13)	4/13 (31)
By 12 months	38/63 (60)	28/35 (80)	1/1 (100)	8/24 (33)	5/21 (24)	0/1	1/7 (14)	4/11 (36)
BID	(N = 40)‡	(N = 19)‡	(N = 1)‡	(N = 19)‡	(N = 26)‡	(N = 2)‡	(N = 10)‡	(N = 13)‡
By 6 months	13/34 (38)	9/15 (60)	0/1	3/17 (18)	4/18 (22)	0/1	1/6 (17)	3/11 (27)
By 12 months	18/34 (53)	10/15 (67)	1/1 (100)	6/17 (35)	4/15 (27)	0/1	1/5 (20)	3/9 (33)
QD	(N = 45)‡	(N = 25)‡	(N = 4)‡	(N = 12)‡	(N = 7)‡	(N = 0)‡	(N = 2)‡	(N = 2)‡
By 6 months	18/38 (47)	18/22 (82)	0/3	0/11	1/6 (17)	0	0/2	1/2 (50)
By 12 months	20/29 (69)	18/20 (90)	0/0	2/7 (29)	1/6 (17)	0	0/2	1/2 (50)

* AP denotes accelerated phase, BID twice daily, CML chronic myeloid leukemia, CP chronic phase, QD once daily, and TKI tyrosine kinase inhibitor. Only patients with clearly discernible resistance to or intolerance of their last prior TKI as determined by investigators were included in the analysis.

† N was the number of evaluable patients by 6 or 12 months. See the Assessment of Antileukemic Activity in the Supplementary Methods section for a detailed definition.

‡ N was the number of patients who received ≥1 dose of asciminib.

Table S5. Categorical Response Shift From Baseline in Patients With T315I CP-CML or AP-CML and Treated With Asciminib.*

Post-treatment BCR-ABL1^{IS} by 6 months, %	Baseline BCR-ABL1^{IS}, %				
	≤0.01 (N = 0)	>0.01 to 0.1 (N = 1)†	>0.1 to 1 (N = 2)†	>1 to 10 (N = 6)†	>10 (N = 23)†
All doses, N‡	**0**	**1**	**1**	**6**	**17**
≤0.01	—	1 (100%)			
>0.01 to 0.1		—	1 (100%)	3 (50%)	1 (6%)
>0.1 to 1			—	2 (33%)	1 (6%)
>1 to 10				1 (17%)	3 (18%)
>10					12 (71%)
Low doses, N‡	**0**	**0**	**0**	**4**	**8**
≤0.01	—				
>0.01 to 0.1		—		1 (25%)	
>0.1 to 1			—	2 (50%)	
>1 to 10				1 (25%)	2 (25%)
>10					6 (75%)
High doses, N‡	**0**	**1**	**1**	**2**	**9**
≤0.01	—	1 (100%)			
>0.01 to 0.1		—	1 (100%)	2 (100%)	1 (11%)
>0.1 to 1			—		1 (11%)
>1 to 10				—	1 (11%)
>10					6 (67%)

* AP denotes accelerated phase, BID twice daily, CML chronic myeloid leukemia, CP chronic phase, IS International Scale, and QD once daily.

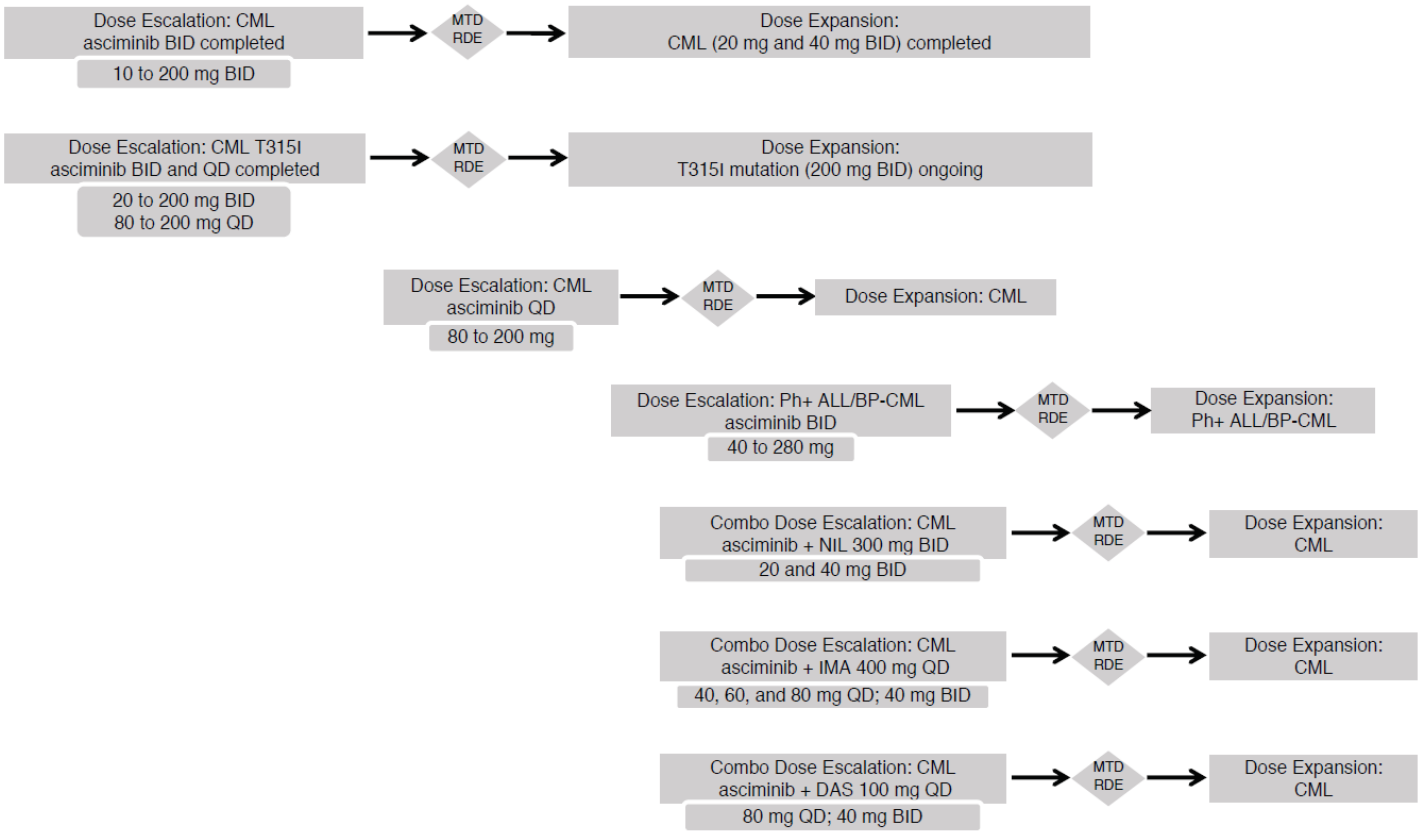
† N was the number of patients who received ≥1 dose of asciminib in each category of BCR-ABL1 transcript level at baseline. This included 27 patients with CP-CML and the T315I mutation and 5 patients with AP-CML and the T315I mutation.

‡ N was the number of evaluable patients in each category of baseline BCR-ABL1 transcript level who had an assessment of molecular response at 6 months following treatment or who achieved a major molecular response within 6 months. See the Assessment of Antileukemic Activity in the Supplementary Methods section for a detailed definition. Percentages were

calculated based on N. One patient with T315I and CP-CML at 150 mg BID had a missing BCR-ABL1^{IS} % value at baseline. Response assessments were reported only for patients with the b2a2 and/or b3a2 transcripts. High doses included ≥150 mg BID, ie, 150 mg BID, 160 mg BID, and 200 mg BID; low doses included doses <150 mg BID, ie, 10 mg to 80 mg BID and 80 mg to 200 mg QD.

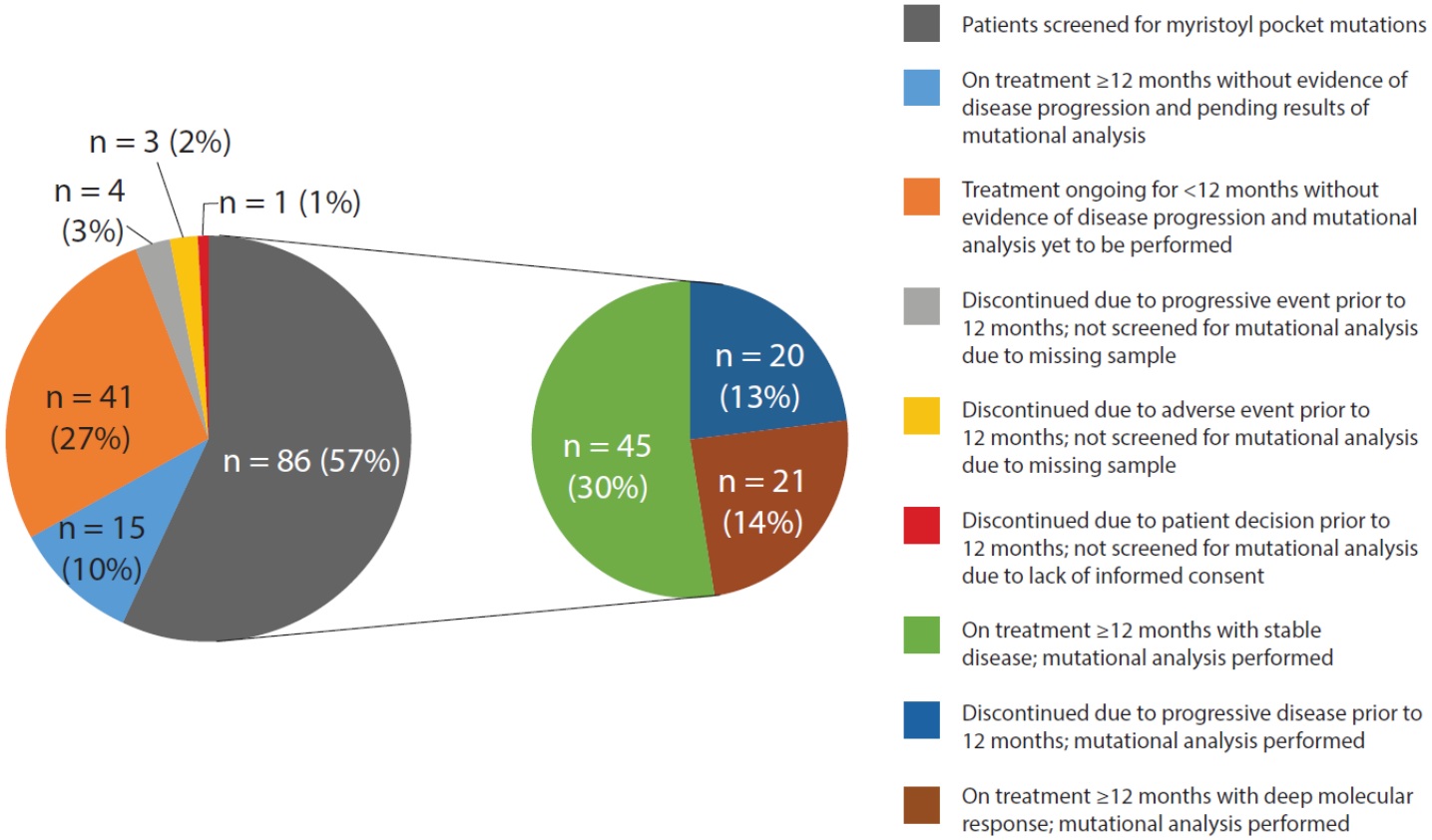
Supplementary Figures

Figure S1. Expanded First-in-Human Study Schema.



ALL denotes acute lymphoblastic leukemia, BID twice daily, BP blast phase, CML chronic myeloid leukemia, DAS dasatinib, IMA imatinib, MTD maximum tolerated dose, NIL nilotinib, Ph+ Philadelphia chromosome positive, QD once daily, and RDE recommended dose for expansion.

Figure S2. Patients With CP-CML or AP-CML Screened to Date for Myristoyl Pocket Mutations.



AP denotes accelerated phase, CML chronic myeloid leukemia, and CP chronic phase.

Figure S3. Bayesian Logistic Regression Model Inferential Results for Asciminib (dose-determining set).

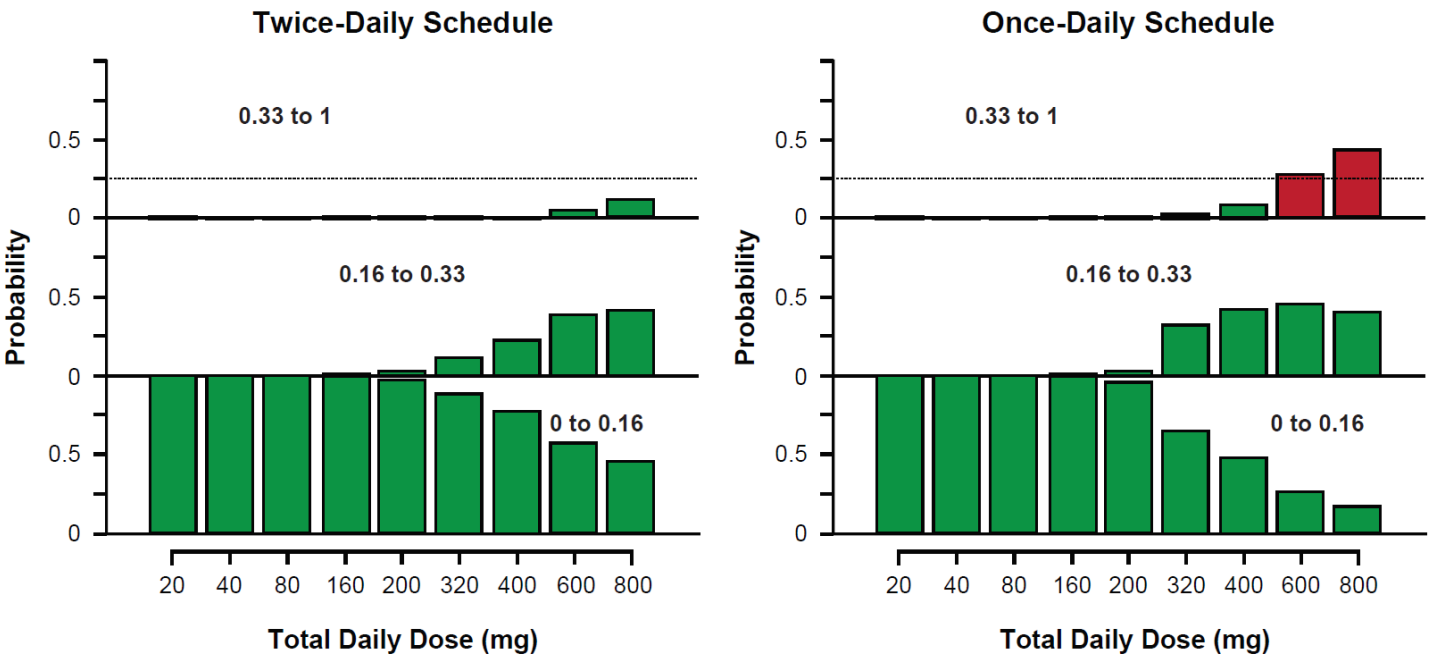


Figure S4A. Mean (SD) Concentration-Time Profiles on a Twice Daily (BID) Monotherapy Schedule.

The mean (SD) concentration-time profiles of asciminib are shown during a 12-hour period in patients on day 15 after dosing with asciminib. Dose groups and the number of patients who could be evaluated in each group were as follows for the BID dose: 10 mg, 1 patient; 20 mg, 5 patients; 40 mg, 12 patients; 80 mg, 11 patients; 150 mg, 12 patients; 160 mg, 2 patients; 200 mg, 6 patients. Dots represent the mean, and the bar represents the SD.

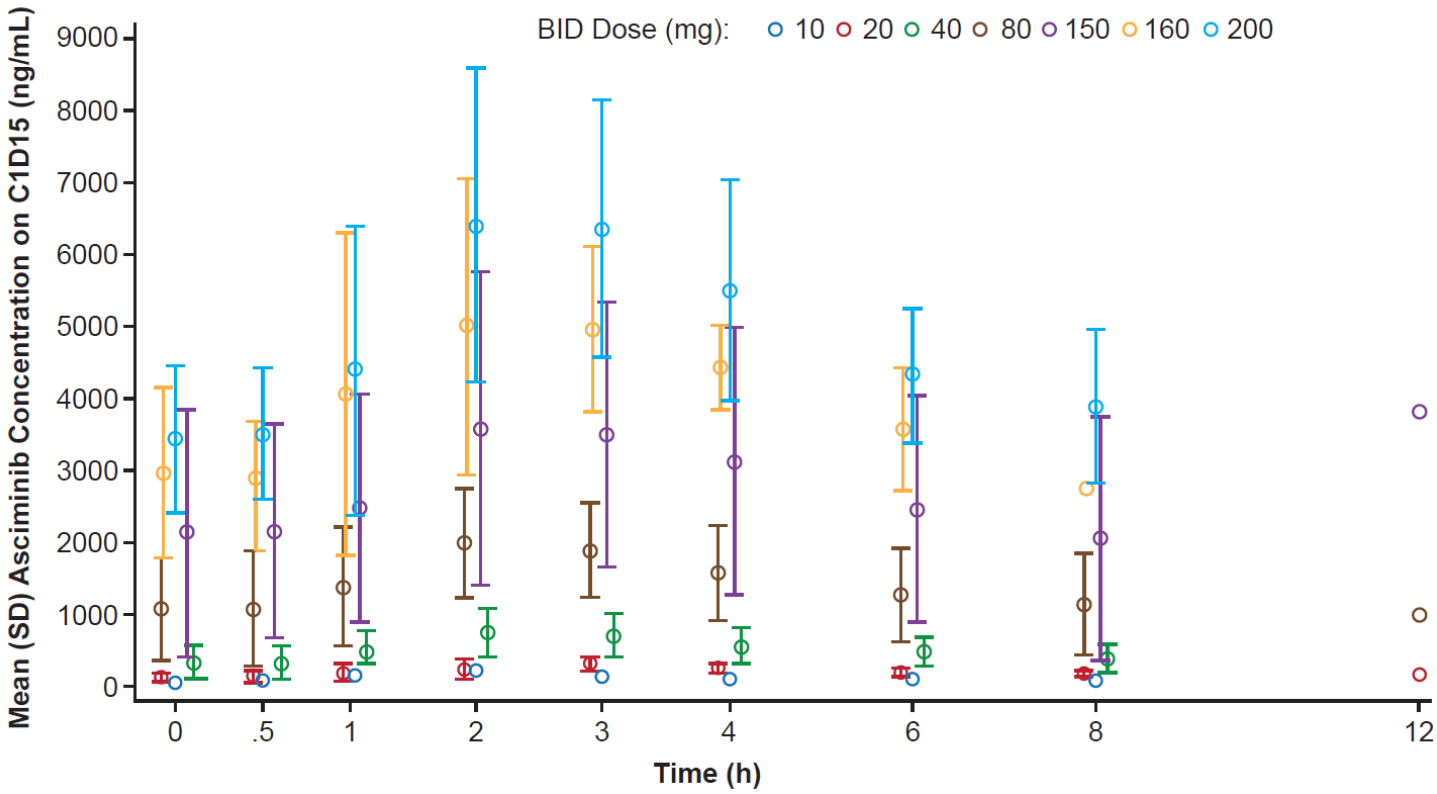


Figure S4B. Mean (SD) Concentration-Time Profiles on a Once Daily (QD) Monotherapy Schedule.

The mean (SD) concentration-time profiles of asciminib are shown during a 24-hour period in patients on day 15 after dosing with asciminib. Dose groups and the number of patients who could be evaluated in each group were as follows for the QD dose: 80 mg, 12 patients; 120 mg, 15 patients; 200 mg, 7 patients. Dots represent the mean, and the bar represents the SD.

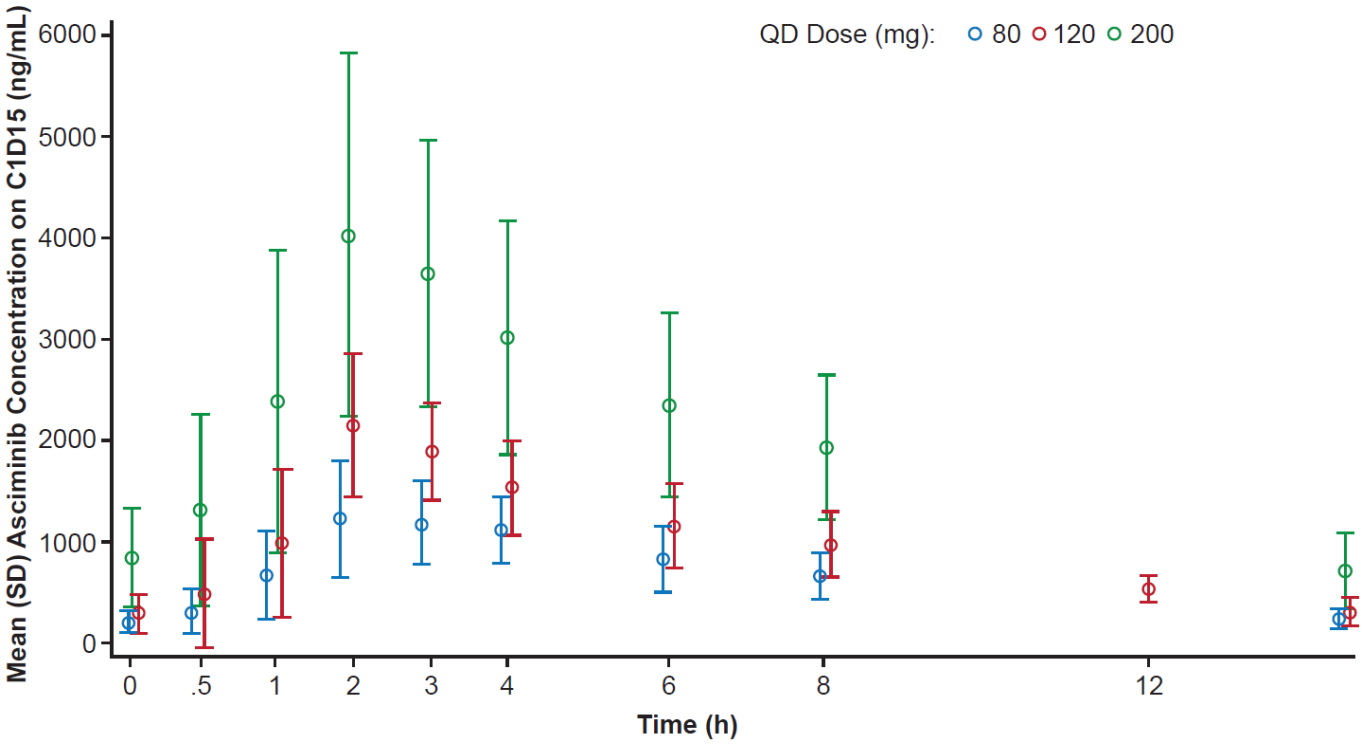


Figure S5. Development of Myristoyl Pocket Mutations in BCR-ABL1 in Four Patients.

The development of myristoyl pocket mutations in BCR-ABL1 are noted in 4 patients with chronic-phase or accelerated-phase chronic myeloid leukemia (CML) treated with asciminib monotherapy on either a QD or BID schedule. The dose-related molecular response (MR) is shown for each of the patients who were undergoing dose escalation, with changes in BCR-ABL1 transcripts—shown as the ratio of BCR-ABL1 to ABL1 (as expressed on the International Scale [IS]) over time (Hughes T, Deininger M, Hochhaus A, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 2006;108:28-37). Dashed vertical lines represent the time of intrapatient dose escalation. BCR-ABL1 myristoyl pocket mutations were assessed by bidirectional Sanger and next-generation sequencing. Baseline assessment of BCR-ABL1 mutational status, presence of Philadelphia chromosome–positive metaphases in the bone marrow (as determined by G-band karyotyping), and history of prior catalytic tyrosine kinase inhibitors (TKIs) administered are provided for each patient. MMR denotes major molecular response.